THE ALLEGED DETOXICATING POWER OF THE THYROID GLAND*

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In 1902 Remedi[1] reported that the injection of extracts of killed cultures of Bacillus prodigiosus, B. anthracis, B. diphtheriae, and B. tetanus uniformly into the two lobes of the thyroid gland, brought about an increased secretion of colloid and averted, or greatly ameliorated, the symptoms of intoxication usually produced by the injection of these bacterial extracts subcutaneously.

Since the literature contains conflicting statements with regard to the action of the thyroid gland in different toxemias, I have carried out series of experiments somewhat similar to those of Remedi. Two series of experiments were undertaken. In the first series, minimal, subminimal, and repeated subminimal lethal doses of diphtheria toxin were injected uniformly into one, and into both thyroid glands of the dog. In the second series tetanus toxin was injected in the same way.

HISTORICAL REVIEW

That secretory epithelium, especially that of the thyroid gland, is remarkably sensitive to toxic bacterial products is well known, but whether this brings about increased secretory activity on the part of the thyroid gland is not so certain. Galleotti[2] found that toxic products of metabolism, when injected into the peritoneal cavity of the turtle, brought about a more marked secretion in the thyroid gland. von Blum[3] is of the opinion that the thyroid neutralizes certain toxic substances in the blood, and he asserts that the presence of such toxic products constitutes the normal stimulation of the cells of the thyroid gland to secretory activity and hypertrophy. Roger and Garnier[4] state that in the acute infectious diseases there is a hypersecretion with an increased amount of colloid in the thyroid gland. In the more chronic diseases, as tuberculosis and typhoid fever, they found a disappearance of colloid, associated with proliferation of the epithelium of the thyroid gland. Torri[5] in similar studies came to the same conclusions. These results could not be confirmed by Kaschwamura.[6]

Many investigators claim, on the other hand, that the parenchymatous

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[1] Sperimentale, 1902, 56, p. 500.

[2] Internat. Monatschr. f. Anat. u. Physiol., 1895, 12, p. 513. Arch. f. Microscopic Anat., 1896, 48, p. 305.

[3] Virchows Arch. f. path. Anat., 1899, 158, p. 495.

[4] Compt. rend. Soc. de biol., 1898, 50, pp. 873, 889. Presse méd., 1899, 7, p. 181.

[5] Policlinico, 1900, n, 6, 8, 10.

[6] Virchows Arch. f. path. Anat., 1901, 166, p. 373.

changes predominate over the colloid changes. They believe that many outside influences will bring about hyperplastic changes. Marine[7] has shown in the brook trout how easily the thyroid gland is changed from a colloid gland to a hyperplastic gland by overfeeding, by unsuitable food, by overcrowding, or by other unhygienic factors, and that the condition can be readily cured or prevented by improving and changing these conditions. McCarrison[8] also found that inanition, unhygienic surroundings, or poor food favor a bacterial toxemia from the gastro-intestinal tract, which induces secondary, that is hyperplastic, changes in the thyroid gland. More recently Bensley[9] showed that the spontaneous hyperplasia of the thyroid gland in the opossum can be produced and controlled by diet alone.

Farrant[10] found marked changes in the thyroid glands of over 700 persons dying of various infectious diseases. He claims that the rapidity of the transformation of a normal thyroid gland into a hyperplastic gland depends not only upon the acuteness and the duration of the infection, but also upon the kind of infection. Farrant produced hyperplasia experimentally by subcutaneous injection of diphtheria toxin. Feeding desiccated thyroid gland along with injection of diphtheria toxin decreased the toxicity of the diphtheria toxin, the animals thus fed surviving, by one or two days, those that were not so fed. Emge,[11] on the other hand, by using lethal and sublethal doses of diphtheria toxin, could not produce any parenchymatous changes in the thyroid gland similar to those observed by Farrant. Furthermore, Emge by producing experimental diphtheria toxemia, could not induce changes in the thyroid gland similar to those observed in the human thyroid gland in cases of fatal diphtheria.

The relation of the thyroid gland to the formation of antibodies and immunity has also been studied. Fassin[12] observed a diminution in the hemolytic and the bacteriolytic alexins of the blood after thyroidectomy. Marbe[13] concluded that hyperthyroidism, induced by feeding desiccated thyroid extract to rabbits and guinea-pigs, distinctly augmented the opsonic power of the blood serum. In a later paper Marbe reported a decrease of the opsonic and phagocytic powers of the blood in thyroidectomized dogs. Frouin[14] partially confirmed Fassin's work relative to the diminution of the alexins in the blood after thyroidectomy in dogs. However, he did not notice any decrease in the amount of tetanus antitoxin in the blood serum of thyroidectomized dogs which had been immunized against tetanus toxin. Furthermore, Lerde and Diez[15] found that thyroidectomized guinea-pigs are about as resistant to diphtheria and tetanus toxin as normal guinea-pigs. Fjeldstad[16] did not observe any difference in the degree of immunity and the rapidity of appearance of the agglutinins for the typhoid bacillus in rabbits immunized after removal of the thyroid glands. More recently Launoy and Levy-Bruhl[17] reported that the removal of the thyroid glands in chickens had no effect on the course of a spirochetal infection (Spirochetosis gallinarum).

[7] Bull. Johns Hopkins Hosp., 1910, 21, p. 95.
[8] Indian Jour. Med. Research, 1914, 2, p. 183.
[9] Am. Jour. Anat., 1916, 19, pp. 37, 57.
[10] Brit. Med. Jour., 1914, 1, p. 470. Lancet, 1913, 2, p. 1820.
[11] Jour. Infect. Dis., 1915, 17, p. 369.
[12] Compt. rend. Soc. de biol., 1907, 62, p. 647.
[13] Ibid., 1908, 64, pp. 1058, 1113.
[14] Ibid., 1910, 69, p. 237.
[15] Gior. d. r. Accad. di med. di Torino, 1905, 11, pp. 195, 429.
[16] Am. Jour. Physiol., 1910, 26, p. 72.
[17] Ann. de l'Inst. Pasteur, 1915, 29, p. 213.

EXPERIMENTS WITH DIPHTHERIA TOXIN

The minimal lethal dose of diphtheria toxin (the amount required to kill a 250-gm. guinea-pig in 5 or 6 days) was found to be 0.004 c.c. This was used as a standard dilution. All dilutions were made with sterile physiologic salt solution (0.85%).

Controls.—Healthy dogs were selected for all the experiments, care being taken to exclude those with visible or palpable evidence of enlarged thyroid glands. The dogs weighed approximately 8 kilos each. It was found that the minimal lethal dose of diphtheria toxin per kilo of body weight of the dog was practically the same as that for the guinea-pig. The calculated dose was diluted with physiologic salt solution to 2.5 c.c. This was injected subcutaneously about the region of the thyroid gland. The onset of symptoms in all the controls was very much the same. The dogs refused all food on the 2nd day. Respiration and pulse rates rapidly increased. Rectal temperature was from 2 to 4 degrees above normal. Death occurred on the 4th day in 2 cases and on the 5th day in 1 case. The thyroid glands were removed and carefully weighed. Thyroid tissue was removed from the center of both the right and left of the gland for histologic examination. All sections were fixed in formalin-Zenker, imbedded in celloidin, and stained with hematoxylin and eosin. Sections taken through the center of the two glands are for practical purposes very similar in histologic structure. This fact is taken into consideration in later experiments when the two glands were compared after one of them had been injected with diphtheria or tetanus toxin. The amount and stainability of the colloid and the presence of hemorrhages and necrosis were especially noted. The type of epithelium and any evidence of active hyperplasia and mitosis were also noted. The results are given in Table 1. The thyroid glands in the control dogs had a normal amount of colloid, the amount of parenchymatous tissue was normal, and the epithelium was of the cuboidal type. No mitosis or any other sign of active hyperplasia was observed.

Minimal Lethal Doses Injected Into Both Glands.—Two dogs were weighed and prepared for operation. Ether anesthesia was used in all cases. The thyroids were exposed through the usual midline incision. The minimal lethal doses were carefully calculated and the dilutions so made that the entire amount injected into both thyroid glands would not be more than 2.5 c.c. The calculated dose was injected as diffusely as possible with the least possible traumatism. The glands were immediately put back in place and the wound closed.

The onset of symptoms was more pronounced and rapid than in the controls. Death occurred from 1 to 2 days sooner than in those injected subcutaneously. Autopsy revealed the usual hemorrhage in the gastro-intestinal tract. The wound about the thyroid gland was healing and there was no evidence of any infection. There was some edema about the thyroid glands but no hemorrhage. The glands were congested, edematous, and had a swollen appearance, but were approximately equal in weight (see Table 1). Microscopic examination: Alveoli of normal size. Colloid stained uniformly. No evidences of an increased formation of colloid. No necrosis. Desquamation of epithelial cells from the walls of the alveoli was most marked in the thyroid gland of Dog 5.

Subminimal Lethal Doses Injected Into Left Gland.—Subminimal lethal doses (one-tenth of the minimal lethal dose) were injected as diffusely as possible into the left thyroid gland. The dogs developed only slight passing symptoms of toxemia. Dogs 3 and 7 were killed with ether on the 7th and 10th

TABLE 1

RESULTS ON THYROID GLAND ACTIVITY OF INJECTION OF DIPHTHERIA TOXIN

Dog	Weight (kilos)	Amount Injected (c.c.)	Site of Injection	Repeated Injections	Date of Death
1	7.9	2.5 = M.L.D.	Subcutaneously about thyroid gland		4th day
2	7.8	2.5 = M.L.D.	Subcutaneously about thyroid gland		5th day
3	8.9	2.9 = M.L.D.	Subcutaneously about thyroid gland		4th day
4	6.2	1.5 = M.L.D.	Both thyroid glands, diffusely		3rd day
5	6.9	1.9 = M.L.D.	Both thyroid glands, diffusely		3rd day
6	7.8	1.9 = 1/10 M.L.D.	Left thyroid gland, diffusely		Killed, 4th day, with ether
7	8.5	1.2 = 1/10 M.L.D.	Left thyroid gland, diffusely		Killed, 7th day
8	8.0	1 = 1/10 M.L.D.	Left thyroid gland, diffusely	Repeated in 15 days	Killed, 21st day
9	7.5	1.5 = 1/10 M.L.D.	Left thyroid gland, diffusely	Repeated in 15 days	Killed, 21st day, with ether
10	8.5	1.8 = 1/10 M.L.D.	Left thyroid gland, diffusely	Repeated in 15 and 30 days	Killed after 6 weeks
11	9.5	2.5 = 1/10 M.L.D.	Left thyroid gland, diffusely	Repeated in 15 and 30 days	Killed after 6 weeks
12	8.6	1.8 = 1/10 M.L.D.	Left thyroid gland, diffusely	Repeated in 15 and 30 days	Killed after 6 weeks
13	9.4	2 = 1/10 M.L.D.	Left thyroid gland, diffusely	Repeated in 15 and 30 days	Killed after 6 weeks
14	7.5	1.5 = 1/10 M.L.D.	Both thyroid glands, diffusely	Six repeated injections	Killed after 3 months
15	8.4	1.8 = 1/10 M.L.D.	Both thyroid glands, diffusely	Six repeated injections	Killed after 3 months
16	8.0	10 = M.L.D.	Liver, diffusely		2nd day
17	8.5	10 = M.L.D.	Spleen, diffusely		2nd day
18	9.5	3 = M.L.D.	Testicle, diffusely		4th day

days respectively. The left glands were increased in weight (see Table 1), edematous and hemorrhagic. Microscopic examination: Colloid in the injected glands was the same in amount as in the normal glands, stained uniformly, and did not distend the alveoli. Few small foci of hemorrhages found. Epithelium of the cuboidal type. Some desquamation of the epithelial cells from the walls of the alveoli. No evidence of any recent active hyperplasia of the epithelial cells. No mitoses.

Repeated Subminimal Lethal Doses Injected Into Left Gland.—Repeated subminimal lethal doses (one-tenth of the minimal lethal dose) of diphtheria toxin were injected as diffusely as possible into the left thyroid. In Dogs 8 and 9 the injections were repeated in 15 days. One of the dogs was killed with ether 21 days after the first injection and the other 30 days after the first injection. The injected thyroid glands showed an increase in weight (see Table 1). Microscopic examination: Marked hemorrhage, edema, and desquamation of epithelium in the injected glands. Less colloid than in the right glands, which were not injected. The colloid did not stain uniformly in the glands that were injected. No evidence of any beginning of active hyperplasia of epithelium. No mitosis of epithelium.

In Dogs 10, 11, 12, and 13 the injections were repeated in 15 and 30 days, and the dogs killed in 6 weeks after the initial injection. The increase in weight

TABLE 1 (Continued)
RESULTS ON THYROID GLAND ACTIVITY OF INJECTION OF DIPHTHERIA TOXIN

Weight of Thyroid Gland		Histologic Description of Thyroid Glands
Right (gm.)	Left (gm.)	
3.6	3.5	Colloid type. Normal
4.2	3.9	Colloid type. Normal
8.5	8.0	Colloid-moderate hyperplastic (reverting) type. Normal
7.6	7.0	Colloid type. Some hemorrhage. No mitosis. No increase in colloid
4.6	5.0	Hyperplastic type. Little colloid. Edema. Hemorrhage. Desquamation
4.2	5.4	Hyperplastic type. Little colloid. Left: hemorrhage. Little colloid. Some desquamation of epithelium
6.2	8.8	Colloid-moderate hyperplastic type. Left: hemorrhages. No other changes
4.6	4.8	Colloid-moderate hyperplastic type. Left: hemorrhage. Edema. Desquamation of epithelium. Less colloid
8.5	10.8	Colloid-moderate hyperplastic type. Left: desquamation of epithelium. Less colloid. Small blood vessels
5.0	4.8	Colloid type. Left: no colloid. Desquamation of epithelium. Many small blood vessels
3.8	5.2	Colloid-slight hyperplastic type. Left: no colloid. No increase but desquamation of epithelium. Small blood vessels
4.6	4.9	Colloid-moderate hyperplastic type. Left: no colloid. Desquamation of epithelium
3.5	3.3	Colloid-moderate hyperplastic type. Left: less colloid. Desquamation. Hemorrhage
4.2	4.0	Colloid-moderate hyperplastic type. Little colloid. Desquamation of epithelium
9.8	9.6	Hyperplastic type. Little colloid. Marked desquamation
6.2	6.7	Colloid type. No changes
9.4	11.6	Colloid-moderate hyperplastic type. No changes. Some desquamation of epithelium.
8.6	8.5	Colloid-slight hyperplastic type. Some desquamation of epithelium

of the injected glands (left) over the glands which were not injected is not so marked in these cases. In 2 only, was there any increase in weight. Microscopic examination: Marked decrease of colloid. Colloid did not take the stain uniformly. Many of the alveoli empty and shrunken. Desquamated epithelial cells scattered about the empty alveoli. No evidence of any recent active hyperplasia of epithelium. No mitosis.

In Dogs 14 and 15, subminimal lethal doses of diphtheria toxin were injected 6 times at intervals of 2 weeks. Both dogs were killed with ether 10 days after the last injection, and the thyroid glands were removed for histologic examination. There was no evidence of any infection about the thyroid glands. Microscopic examination: Marked decrease in the amount of colloid in all the sections. Many of the alveoli were empty, and the colloid that was still left in the alveoli did not take the stain uniformly. Desquamation of epithelium from the walls of the alveoli marked, but no evidence of any active hyperplasia on the part of the epithelial cells. No mitosis. In the thyroid glands of Dog 15 there was practically no colloid. The epithelium of many of the alveoli had entirely desquamated, and these cells were scattered about the empty alveoli. No evidence of any active hyperplasia. No mitosis.

Minimal Lethal Dose Injected Into Liver, Spleen, and Testicles.—Minimal lethal doses of diphtheria toxin were injected diffusely into liver, spleen, and

TABLE 2
RESULTS ON THYROID GLAND ACTIVITY OF INJECTION OF TETANUS TOXIN

Dog	Weight (kilos)	Amount Injected (c.c.)	Site of Injection	Repeated Injections	Date of Death
1	8.5	2.5 = M.L.D.	Subcutaneously about thyroid gland		5th day
2	7.4	2.5 = M.L.D.	Subcutaneously about thyroid gland		5th day
3	9.0	2.5 = M.L.D.	Subcutaneously about thyroid gland		4th day
4	8.0	2.5 = M.L.D.	Both thyroid glands, diffusely		6th day
5	7.8	2.5 = M.L.D.	Both thyroid glands, diffusely		5th day
6	8.5	1.2 = M.L.D.	Left thyroid gland, diffusely		6th day
7	9.0	2.5 = 1/10 M.L.D.	Both thyroid glands, diffusely		Killed, 20th day
8	8.4	1.5 = 1/10 M.L.D.	Left thyroid gland, diffusely	Repeated in 15 days	Killed, 20th day
9	8.8	1.5 = 1/10 M.L.D.	Left thyroid gland, diffusely	Repeated in 15 and 30 days	Killed, 40th day
10	8.0	2.5 = 1/10 M.L.D.	Both thyroid glands, diffusely	Repeated in 15 days	Killed, 30th day
11	8.6	2.5 = 1/10 M.L.D.	Both thyroid glands, diffusely	Repeated in 15 and 30 days	Killed, 40th day

testicles, respectively, in 3 dogs. The onset of symptoms was earlier and their severity more marked than after the subcutaneous injections. Death occurred in from 48 to 72 hours. The results are given in Table 1. Colloid present in all the glands; glands in various stages of normal hyperplasia. Active hyperplasia or mitosis not observed. Slight desquamation of the epithelial cells, otherwise no noteworthy changes.

EXPERIMENTS WITH TETANUS TOXIN

The tetanus toxin was kept in dry form, as solutions of tetanus toxin are rapidly destroyed by exposure to light, heat, etc., even when allowed to stand under ordinary conditions.[18]

Normal healthy dogs were used in all the experiments. The minimal lethal dose (the amount of tetanus toxin that kills a 300-gm. guinea-pig in 4 days)[19] was found to be.0.00001 gm. This is much larger than that for proportionate weight of guinea-pigs. The latter, when injected subcutaneously in the region of the thyroid gland, was not fatal for 18 or 20 days. The dose was gradually increased to 2.8 times the calculated minimal lethal dose of the proportionate weight of guinea-pig. Such a dose of tetanus toxin was fatal in from 4 to 5 days. This was used as a standard and all calculations for subsequent injections were made on this basis.

That tetanus toxin possesses a strong affinity for the cells of the central nervous system has been shown clearly by Wassermann and Takaki.[20] Later, Meyer and Ransom[21] pointed out that the action and the onset of the symptoms following the injections of tetanus toxin depend on the distance the

[18] Kolle and Wassermann, Handb. d. pathogen, Microorganismen, 1913, 4, p. 983.

[19] Rosenau and Anderson, Public Health Bull. 43, Washington, D. C. Bull. 43, Hyg. Lab., Washington, D. C.

[20] Berl. klin. Wchnschr., 1898, 35, p. 5.

[21] Arch. f. exper. Path. u. Pharmakol., 1903, 49, p. 369.

TABLE 2—(Continued)
RESULTS OF THYROID GLAND ACTIVITY OF INJECTION OF TETANUS TOXIN

Weight of Thyroid Gland		Histologic Description of Thyroid Glands
Right (gm.)	Left (gm.)	
8.0	8.5	Colloid-moderate hyperplastic type. Normal
3.8	4.2	Colloid type. Normal
6.8	6.4	Colloid type. Normal
4.4	4.1	Colloid-marked hyperplastic type. Hemorrhages. Desquamation of epithelium. Colloid partly absorbed. Vacuoles
3.6	3.8	Colloid-slight hyperplastic type. Desquamation of epithelium (slight)
5.8	7.2	Colloid type. Left: some hemorrhage. Less colloid?
8.6	8.8	Colloid-marked hyperplastic type. Alveoli shrunken. Less colloid. Some desquamation of epithelium
6.5	9.2	Colloid-slight hyperplastic type. Left: hemorrhage. Desquamation of epithelium. Alveoli shrunken, empty. Less colloid
6.4	8.2	Colloid-marked hyperplastic type- Left thrombus. Hemorrhage. Little colloid. Marked desquamation
8.0	8.2	Colloid-marked hyperplastic type. Alveoli shrunken. Little colloid. Irregular. Desquamation of epithelium
9.2	9.5	Colloid-moderate hyperplastic type. Hemorrhage. Alevoli shrunken. Amount of colloid decreased. Marked desquamation of epithelium

toxin has to travel along the motor nerve sheaths to reach the ganglion cells of the central nervous system, and that such results would vary to a certain extent with the location of the injection and the proximity and the amount of nervous tissue present at the site of the injections. In these experiments the amount to be injected was dissolved in 2.5 c.c. of physiologic salt solution. The results and data are give in Table 2.

Controls.—Three dogs were weighed and the calculated minimal lethal dose of tetanus toxin was injected into the subcutaneous tissue in the region of the thyroid gland. Twitching and stiffness of the muscles appeared on the 3rd day, followed by typical convulsions within the next 24 hours. Convulsions seldom lasted more than 24 hours before death. The thyroid glands were removed immediately after death and sections prepared for microscopic examination. Glands of the colloid type. The colloid took the stain uniformly. No desquamation or active hyperplasia of the epithelium. No mitosis of the epithelium.

Minimal Lethal Dose Injected Into Both Thyroid Glands.—Three dogs of approximately uniform size were weighed and prepared for operation. In Dogs 4 and 5 the calculated dose was injected into both thyroid glands as diffusely as possible with the least possible traumatism, and the wound closed with the usual aseptic precautions. In Dog 6 the calculated dose was injected into the left thyroid gland. The results are given in Table 2. The symptoms of tetanus appeared from the 4th to the 5th day. This is from 24 to 48 hours later than in the control animals which were injected subcutaneously in the region of the thyroid gland. These symptoms were followed by the usual typical convulsions and death within the next 24 hours; that is, from the 5th to the 6th day. In Dog 6 the injected gland (left) was considerably increased in weight. The classification of the glands as to type, in accordance with the microscopic examination and other data, is given in Table 2. Microscopic examination: Multiple hemorrhages in the injected thyroid glands.

No necrosis in any of the sections. No change in the amount or in the staining properties of the colloid. Some desquamation of the epithelium from the walls of the alveoli, but no evidence of any active hyperplasia in the injected glands. No mitosis of epithelium.

Repeated Subminimal Lethal Doses.—Repeated subminimal lethal doses ot tetanus toxin were injected diffusely into the thyroid glands of 5 dogs. In Dogs 7, 10, and 11, the injections were made into both the right and left thyroid glands. These injections were repeated at intervals of 2 weeks. For these subsequent injections the thyroid glands were always exposed under ether anesthesia through an incision made in the scar tissue of the previous operation. The dogs were killed with ether at intervals ranging from 20 to 40 days after the initial injection. In Dogs 8 and 9 the injections were made only into the left thyroid gland. The data are given in Table 2. The injected thyroid glands were increased in weight. Microscopic examination: Marked decrease in the amount of colloid in the injected (left) glands. Many of the alveoli had no colloid but were partly filled with desquamated epithelial cells. Some hemorrhage and edema in some of the sections. No evidence of any active hyperplasia of the epithelium. No mitosis.

DISCUSSION OF THE RESULTS

It is evident that my results do not confirm the reports made by Remedi. He stated that the injection of diphtheria and tetanus toxin directly into the thyroid gland stimulated the thyroid glands to an increased formation of colloid which neutralized the action and decreased the symptoms produced by these toxins. I found that the minimal lethal dose of diphtheria toxin was invariably fatal in from 1 to 2 days sooner than when injected subcutaneously. This was presumably due to the more rapid entrance of the toxin into the circulation when injected directly into the vascular gland. In the case of tetanus toxin, the dogs that were injected diffusely in the thyroid gland survived those injected subcutaneously in the region of the thyroid gland by 1 or 2 days. There were no evidences of any histologic changes or any activity of the thyroid gland to account for this apparent decrease in toxicity on the part of the tetanus toxin when injected directly into the thyroid gland. Probably the more rapid absorption of the toxin into the blood when injected directly into the thyroid gland would cause more of the tetanus toxin to be bound in such organs as the liver, kidney, and spleen, or there may be fewer routes of travel along motor nerve sheaths from the thyroid gland.

The early increase in weight noticed in the thyroid glands that were injected is explained by the congestion and edema following the injection. There were no changes in the amount of colloid or in the character of the epithelium following single injections. It was only after a few repeated injections that a decrease occurred in the amount of colloid. Six repeated subminimal lethal doses when injected diffusely into the thyroid gland during a period of 3 months caused nearly com-

plete absorption of the colloid. This indicates that the colloid in the alveoli is absorbed under certain conditions, but this absorption does not take place as rapidly as some have contended. According to Bensley,[9] the colloid in the alveoli represents a reserve supply of the product of the internal secretion of the thyroid gland, and this supply may be slowly absorbed when the normal production by the epithelial cells is decreased by such conditions as cachexia, toxemia, etc. Probably under the conditions established here, when the glands are injected repeatedly with the diphtheria and tetanus toxin, the epithelial cells are exposed to a repeated intoxication. Under such conditions, there would be a decrease in the active production of colloid by the epithelial cells, so that a gradual absorption of the reserve supply of colloid takes place.

Active hyperplastic changes were not found in any of the thyroid glands. This even applies to those glands which were injected as many as 6 times. These results agree with those of Emge.[11] There was a marked desquamation of the epithelium, especially noticeable in those thyroid glands which were injected repeatedly with subminimal lethal doses of diphtheria and tetanus toxin. This was presumably due to the continual intoxication and traumatism following these injections.

SUMMARY

The thyroid gland has no detoxicating properties that can be demonstrated by the injection of diphtheria and tetanus toxin directly into the thyroid gland.

A minimal lethal dose of diphtheria toxin, when injected into the thyroid gland, killed from 1 to 2 days sooner than when injected into the subcutaneous tissue.

The symptoms were just as marked in those dogs injected directly in the thyroid gland as in those which were injected subcutaneously.

The injected gland showed an increase in weight in early fatal cases due to congestion and edema.

Microscopic examination did not show any increase in the secretion of colloid as Remedi stated. Repeated injections into the thyroid gland caused an absorption of the colloid from the alveoli.

Active hyperplastic changes of the epithelium as described by Farrant were not evident in these glands. This was true both after single and repeated injections into the thyroid gland.

Repeated subminimal lethal doses of diphtheria and tetanus toxin, when injected diffusely into the thyroid gland, caused a desquamation of the epithelium from the walls of the alveoli.